Aged EFAD mice as a model for the effects of APOE and sex on AD pathology

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Research Abstract

The APOE ?4 allele of apolipoprotein E (apoE) is the greatest genetic risk factor for Alzheimer's disease (AD) and is associated with accelerated amyloid-? peptide (A?) accumulation both as amyloid and soluble oligomeric A? (oA?), the latter considered a proximal neurotoxin. Importantly, female ?4 carriers have a greater lifetime risk for developing AD, an increased rate of cognitive decline and accelerated accumulation of A? compared to male carriers. Similarly, female familial AD (FAD)-Tg mice have greater cognitive deficits and increased A? pathology than male mice. The link between APOE4 and AD risk is likely multi-factorial and remains poorly understood; while the increased risk for female ?4 carriers remains virtually unexplored. As

sporadic AD represents ?98% of cases, with age the key risk factor, the UH2 phase of this proposal will test the hypothesis that aged EFAD mice develop profound AD pathology, significantly influenced by APOE genotype and sex. To study the interaction between human APOE (h-APOE) and AD pathology, we developed EFAD mice by introducing h-APOE into 5xFAD-Tg mice. By 6 months (M), E4FAD mice have greater A?- and tau-pathology, neuroinflammation and cognitive deficits compared to E3FAD. In E4FAD vs. E3FAD, and females vs. males, the levels of amyloid and soluble A? (A?42 and oA?) are greater and apoE/A? complex lower. The critical component uniting these observations into a testable hypothesis is the lipidation state of apoE. ApoE is less lipidated in E4FAD vs. E3FAD brains and in females vs. males. In human brain and CSF, and EFAD mouse brain, apoE lipidation negatively correlates with soluble A?. Thus, for the UH3 phase, our data support the hypothesis that reduced apoE lipidation results in reduced levels of apoE/A? complex, inefficient clearance of soluble A?, synaptic loss, memory and cognitive deficits, and dementia. UH2 Phase: Aim 1: Establish breeding program for 18M EFAD mice and perform benchmark testing for AD pathology. (N=12): APOE4? > APOE4? ? APOE3? > APOE4?. By the end of Year 2, measures will include MWM for behavior, AD pathology by immunohistochemistry (IHC), and biochemistry (BC) including levels of apoE, oA?, A?42. UH3 Phase: Are aging EFAD mice a viable model for the factors effecting AD pathology in humans, particularly APOE genotype and sex, thus providing a model for testing prospective therapeutic interventions and mechanistic hypotheses, including our “apoE lipidation hypothesis”? Aim 2. Establish 10M, 14M (middle age) and 18M (aged) EFAD mouse cohorts to define disease progression by detailed analysis of behavior and tissue for comparison with 6M (adult) (?3 and ?4; ? and ?). Analyses will include multiple cognitive tests, IHC for A?- and tau-pathology neuroinflammation and neuron counts, and BC for extraction profiles of apoE and A?, apoE lipidation, and levels of oA?, A?42, apoE, and apoE/A?. The failure of AD clinical trials questions the predictive validity of preclinical AD-Tg mouse models that lack h-APOE, the major genetic risk factor for AD. However, the greatest risk factor for AD is age; aged EFAD mice will address both these critical risk factors.

Further information available at:

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